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ABSTRACT

The objective of research in contraceptive evaluation is to improve the ability of individuals to choose contraceptive methods best suited to their needs and circumstances and to provide information that will lead to the development of safer and more effective methods. There are usually three considerations in judging the importance of a method of contraception: (1) the number of people using it; (2) its success in regulating fertility; and (3) the mortality and morbidity associated with its use. In this report, five methods of contraception are discussed: oral contraceptives, intrauterine devices, barrier methods, female sterilization, and male sterilization. Each section contains information on the current state of knowledge and directions for future research. High-priority recommendations for research initiatives during the next 5 years are presented in the final summary, along with the general criteria that were considered in developing the recommendations. (JD)

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Contraceptive Evaluation

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SP 020 565

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Contraceptive Evaluation

I. Introduction

Contraception is one of the most widely practiced preventive measures in society. Almost 20 million healthy American women in their reproductive years currently use oral contraceptives (OCs), intrauterine devices (IUDs), and barrier methods, including the diaphragm and vaginal spermicides, or have been sterilized to avoid unwanted pregnancy. In addition, 6 million men have had vasectomies.

It is the mission of the Contraceptive Evaluation Branch of the National Institute of Child Health and Human Development (NICHD) to assess the safety and effectiveness of methods of fertility regulation currently in use in the United States. The program endeavors to clarify and reduce the risks and improve the benefits of fertility-regulating methods. Major emphasis is placed on the detection and evaluation of short-, mid-, and long-term effects on health (adverse or beneficial) that must be weighed with questions of efficacy to assess fully the value of different contraceptive methods. Program activities are focused upon:

- Identification of relationships between contraceptive methods and medical complications;
- Delineation of characteristics or circumstances that place individuals at risk for these complications;
- Evaluation of the mechanisms by which contraceptive methods affect health; and
- Evaluation of the effectiveness of methods.

The objective of research in contraceptive evaluation is to improve the ability of individuals to choose contraceptive methods best suited to their needs and circumstances, and to provide information that will lead to the development of safer and more effective methods. There are usually three considerations in judging the importance of a method of contraception: (1) the number of people using it; (2) its success in regulating fertility; and (3) the mortality and morbidity associated with its use.

In this report five methods of contraception are discussed: oral contraceptives, intrauterine devices, barrier methods, female sterilization, and male sterilization. Each section contains information on the current state of knowledge and directions for future research. High-priority recommendations for research initiatives during the next 5 years are presented in the final summary, along with the general criteria that were considered in developing the recommendations.

II. Oral Contraceptives

For the majority of women who use oral contraceptives (OCs) the advantages of OCs far outweigh the disadvantages. They are the most effective and reliable method of birth control available. They do not interfere with the spontaneity of sexual intercourse and have few immediate adverse effects. Moreover, in some women they offer the additional benefit of alleviating menstrual problems. It is probably because of these advantages that OCs are so widely used. In the United States, they are currently used by approximately 12 percent of the 52 million women of childbearing age. The rate of use has declined over the past 5 years (down from 20 percent in 1975), in part due to concerns about known adverse consequences, but also perhaps because of unjustified fears about their effects on health. Nevertheless, because of the large number of women who have used OCs in the past, as well as the over 6 million who currently use them,[1] their effects on health remain a major public health concern.

Since overall morbidity and mortality are low in young women, it takes many woman-years of use of OCs before conclusions can be drawn regarding their effects on health. Four large epidemiologic studies are being used to evaluate the effects of OC use on morbidity and mortality. They are the Royal College of General Practitioners (RCGP)[2] study and the Oxford Family Planning Association (FPA) study[3] in Britain, and the Kaiser Permanente Study (Walnut Creek)[4] and the Nurses' Health Study[5] in the United States.

Current State of Knowledge

Oral contraceptive use has been found to influence the occurrence of a variety of medical conditions.[1] Women using oral contraceptives, for example, have been reported to have less iron deficiency anemia, fewer benign breast cysts, and fewer ovarian cysts than women not using this method of contraception. Conversely, oral contraceptive use is associated with an increased occurrence of urinary tract infections, gallbladder disease, and certain liver disorders. In addition, there continues to be some concern over the effect of oral contraceptive use on subsequent fertility and on the occurrence of birth defects, although currently available data appear to rule out any important adverse effects in these areas.

The chief causes of morbidity and mortality among OC users are vascular and neoplastic diseases, and each of these may be influenced by oral contraceptive use. Research concerning these two disease categories is therefore of primary concern.

Vascular Diseases

Cardiovascular Disease

Myocardial infarction is by far the leading cause of death among American women, with over 125,000 fatalities each year. Since 1975, reports published from Britain[6,7] have indicated an approximately threefold increase in the risk of both fatal and nonfatal myocardial infarction among current OC users. Numerous other reports from both Britain and the United States have shown similar results.[8] It is the fatal disease most strongly and consistently related to OC use. In studies that have evaluated other cardiovascular risk factors as well, the majority of women who developed myocardial infarction were smokers.[6,8,9] Very few young, nonsmoking women in any of these studies had heart attacks. Results from two descriptive studies using data from Britain[10,11] are consistent with the conclusion that the effects of smoking and OC use are synergistic. One possible mechanism that may be involved in this interaction is the effect of smoking and OCs on high-density lipoprotein cholesterol (HDL-C) levels. It has been demonstrated that some contraceptive preparations lower HDL-C,[12] as does smoking.[13] Low levels of HDL-C have been associated with increased risk of coronary heart disease.[14] These findings, taken together, suggest the possibility of an interaction between the effects of smoking and OC use on HDL-C. If this

interaction were to be established, the extent to which the risk of myocardial infarction among both smoking and non-smoking OC users is due to low levels of HDL-C would need to be quantified.

Cerebrovascular Disease

Subarachnoid hemorrhage, a type of stroke that may be caused by the rupture of congenitally weak cerebral blood vessels, accounts for about one-third of deaths from cerebrovascular disease among women of childbearing age. The RCGP study[2] and the Walnut Creek study[15] have found that both current and past OC uses seem to be associated with increased risks of dying from subarachnoid hemorrhage, although numbers were small in both studies. Moreover, issues such as duration of use and persistence of the increased risk after cessation of use have not been well studied, nor has the possible mechanism of this effect. In any event, because the death rate from this disease is so low in this age group (less than 10 per 100,000), the association between current OC use and hemorrhagic stroke may not be of major public health importance.

The possible association between OC use and other risk factors for stroke, such as hypertension, merits consideration. One study has suggested that the combination of hypertension, OC use, and smoking greatly increases the risk of stroke.[16] Moreover, studies of the relationship between OC use and hypertension have consistently indicated a slight increase in blood pressure among current OC users, which is reversible when use of the pill is discontinued.[17] Because the OC-induced elevation of blood pressure is transient, the important epidemiologic issue may be to determine how much of the excess cerebrovascular disease mortality attributed to OC use is the direct result of hypertension and how much is the result of interactions between OCs and other factors.

Venous Thromboembolism

Thromboembolic disease was one of the earliest conditions reported in relation to OC use. This association is well established,[3,18,19] as evidenced by the warning label that the Food and Drug Administration (FDA) has asked to be attached to OC packages for consumers. The magnitude of risk of thromboembolic disease has been shown to be related to the amount of estrogen in the contraceptive pill.[20] In the last 5 years, increasing proportions of women have been

prescribed lower-dose estrogen preparations, which in public health terms lower the importance of the thromboembolic complications. Although the relative risk of thromboembolism among OC users is high (generally 10 times greater than among nonusers),[3] the condition is so rare in young women that the actual excess risk is quite low.[21] It therefore seems reasonable to conclude that further research into the association between OCs and thromboembolic disease should not be a major priority, although inquiry into basic mechanisms might be fruitful.

OC Formulation and Vascular Disease

Evidence is accruing that the risk of vascular disease among OC users is in part related to OC formulation. As mentioned previously, it is well established that lowering the estrogen content of OC preparations decreases the risk of venous thromboembolism. For arterial disease, there is growing evidence that the amount of progestogen is important.[22,23] Because chemically different progestogens have been found to have different effects on glucose tolerance and lipid levels, the specific type of progestogen may also be important.[24]

Neoplastic Diseases

Breast Cancer

In the United States, 100,000 new cases of breast cancer occur each year. The case fatality rate is about 30 percent, which means that over 30,000 women die from this disease annually, representing approximately 25 percent of all deaths among women over 40 years of age. Most studies have shown that OC users have no significant excess risk of developing this disease.[25] These studies, however, used noncontraceptors as controls, a factor that might affect the results materially. Some nonusers of OCs, for example, may be subfertile or infertile and therefore already be at an increased risk of developing breast cancer. Similarly, women with benign breast disease, which is itself a predictor of breast cancer, may be advised against using OCs because of their condition. Because reports have shown that various subgroups of OC users (such as women with a family history of the disease) are at increased risk of breast cancer, further studies should be done of this relationship in such subgroups defined prior to the conduct of the study.

Other factors such as parity, age at first birth, diagnosis of benign breast disease, and length of exposure to OCs should also be considered, as should the effects of starting OC use at an early age.

Cervical Cancer

The primary risk factors for cervical cancer are age at first intercourse and number of sexual partners.[26] Studies that have evaluated OC use in relation to cervical cancer have generally reported increased risks which are fully explained by the effects of different sexual behavior among users and nonusers.[27] Studies that have not analyzed differences in sexual behavior between users and nonusers have reported different findings, mostly tending toward no association.[3,28] A recent study[29] has suggested that dysplasia was more likely to progress to carcinoma in situ in women who use OCs than in women who do not, particularly in those with longer ($\geq$ 6 years) durations of use. The idea that OCs have a role in promoting but not initiating cervical tumors is one that merits further research.

Uterine Cancer

Studies have suggested that the combination contraceptive pills, which contain progestin, may protect women from developing uterine cancer.[30] The incidence of this disease is so rare in young women, however, that the public health importance of such a protective effect is small. In this context, it is important to note that uterine cancer has not been mentioned in either the RCGP study[31] or the Oxford FPA study.[3] A recent study[32] has suggested that use of sequential pills may be related to an increased risk for this disease, but for that very reason sequential pills were taken off the market prior to publication of the study.

Ovarian Cancer

There is some evidence that OC use may have a protective effect for ovarian cancer.[3,31,33] Several mechanisms have been proposed,[34] but data to evaluate this question are lacking.

Melanoma

Data from the Walnut Creek study have suggested that OC users are more likely than nonusers to develop melanoma, with risks increasing with duration of use.[35] The number of reported cases was small, however, and none of the differences was statistically significant. Moreover, the major risk factor for melanoma is exposure to sunlight, and this was not taken into account. Studies that consider exposure to the sun are needed to obtain more reliable estimates of any association between OCs and the development of melanoma.

Liver Tumors

Although several studies have reported a dramatic increase in risk of developing hepatocellular angioma, as well as adenoma associated with long-term OC use,[36] the incidence of these tumors is extremely low. One estimate is 1 per 250,000 users.[37] Three British studies that have accumulated at least that many women-years of OC use have not identified a single woman with such a tumor.[38] Moreover, benign hepatocellular tumors are most closely associated with high-estrogen OCs, which have been used less frequently in recent years.[36] The fact that adenoma is a premalignant condition raises the possibility that OCs are involved in the development of cancer of the liver. In retrospective data from a cohort of 120,000 nurses in the United States, only two hepatic malignancies were identified, and neither patient had used OCs.[39] In light of this evidence, it is clear that women who use OCs have a very low risk of developing a liver tumor despite the increased risk compared with that of nonusers.

Other Effects of OC Use

The possible relationships of OC use with pituitary adenoma and diabetes mellitus require further evaluation. The suspected relationships with these two conditions are adverse, while preliminary information suggests a beneficial impact of OC use upon rheumatoid arthritis.

Although much has been reported from ongoing studies about minor health effects of OC use,[2,3] most of the information relates to high-dose formulations in the past. Prescribing physicians and their patients would therefore benefit from the accumulation of reliable data about minor health effects in relation to currently marketed OC preparations.

Ongoing Studies

In addition to the four cohort studies mentioned previously,[2,3,4,5] the following investigations are currently in progress.

Neoplastic Diseases

One study ongoing is a population-based, case-control study designed to evaluate comprehensively the relationships between OC use and breast, endometrial, and ovarian cancer. Twenty specific hypotheses have been identified for investigation, and they consider different categories of OC exposure and of possible interactions between OC use and established or hypothesized risk factors for breast, endometrial, and ovarian cancer. The developmental phase of the study has been completed and is ready for implementation. The study is scheduled for completion by 1984.

A study of the association between OC use and the occurrence of specific histopathologic forms of benign breast neoplasia is in progress to evaluate further an earlier finding that OC use is associated with a decreased risk of those forms of the disease that appear to have little malignant potential, but a possible increased risk of the premalignant forms.

A case-control study is being conducted to determine whether OC use increases the risk that women will develop pituitary adenoma. Two case-control studies of the relationship between OC use and the occurrence of malignant melanoma are also in progress.

Vascular Diseases

A case-control study of women hospitalized with first episodes of myocardial infarction was designed to evaluate possible interactions between OC use and other known or hypothesized risk factors for myocardial infarction such as smoking, alcohol use, personality type, diabetes mellitus, and hypertension. Preliminary data from this study indicate that both past and current OC use increases risk of myocardial infarction.

Three studies of the relationship between the use of oral contraceptives and the occurrence of hypertension have been completed. One study found no increase in the prevalence, incidence, or characteristics of hypertension among

OC users. Another found a slight increase in blood pressure that was reversible upon discontinuation of OCs. Data from the third are still being analyzed. A comprehensive review of the methodology and findings of these studies is being considered.

A prospective study is being initiated to evaluate the effect of different OC formulations on serum lipoprotein patterns. Special emphasis will be placed on comparison of formulations containing different progestogens.

Another study in progress suggests that OC usage may result in the formation of an abnormal globulin, perhaps an antibody, found in the serum of some users, and that this protein may be associated with thrombosis. The study also suggests that the level of the protein, which is easily measured, may be used as a predictor of thrombotic complications. Confirmation and expansion of these potentially useful observations are also the objectives of two additional studies being initiated.

Other Sequelae

A case-control study of women with newly diagnosed diabetes mellitus is in progress. The study is designed to determine whether use of contraceptive steroids, which can impair glucose metabolism, increases the risk of developing clinical diabetes. Two case-control studies are under way to assess the risk of infertility or subfertility after use of steroid and other contraception modalities.

Needed Research

From the preceding discussion of the current state of knowledge concerning OCs, two major research priorities emerge: the effects of long-term exposure to OCs; and possible interactions between OCs and other risk factors.

Effects of Long-Term Exposure

Vascular Diseases

Generally, current use of OCs has a greater magnitude of association than past use with increased risk of myocar-

dial infarction,[6,7,8] stroke,[16] thromboembolism,[18] or hypertension.[17] Nonetheless, it is possible that both current and past use may play a role. For example, current use may primarily accelerate thrombogenesis, whereas past use may affect atherogenesis. A test of this hypothesis would require evaluation of women who are already at increased risk of cardiovascular disease because of the presence of thrombogenic and(or) atherogenic risk factors.

Neoplastic Diseases

The analogy with cigarette smoking[40] and other carcinogens suggests that risks may not appear for two or more decades after first exposure to OCs. If this is the case, there are not enough data on long-term OC use to detect an increase in risk of developing certain cancers. A related issue concerns the effects of early exposure to OCs. For example, if OC use in adolescent women affects the development of breast cancer in the same way as other risk factors, such as age at menarche and age at first birth, studies of women who started using OCs as teenagers should be done to detect possible carcinogenic effects.

Interactions With Other Risk Factors

Vascular Diseases

The most important interaction for vascular diseases is that between OC use and cigarette smoking, although relationships with hypertension and with HDL cholesterol may also exist. Most previous studies have not involved sufficiently large numbers of women exposed to OCs for long enough periods of time to allow investigators to quantify such interrelationships. Even for myocardial infarction, which is one of the two leading causes of death in women of reproductive age, mortality is very low. Consequently, many woman-years of observation would be necessary to yield a number of events large enough to allow reliable estimates of the absolute risk of myocardial infarction associated with OC use and cigarette smoking at various ages. The practical importance of such estimates relates primarily to aiding physicians who may wish to counsel individual patients. Preliminary data indicate lower HDL-C levels in both smokers and OC users. To assess whether this effect on HDL-C, if real, is related to the increased incidence of myocardial infarction among women with one or both of these risk factors, a large cohort of women would need to be identified and followed for a long period of time. It would also be

important to include in such a study a sufficient number of black women to examine the relationship of blood pressure and OC use on myocardial infarction and stroke. Black women are more likely to use OCs[41] and also are at greater risk of having hypertension.[42]

Neoplastic Diseases

A major public health interest regarding the relationship of OC use and other risk factors concerns breast cancer. Although most studies show no overall association between OC use and breast cancer, evidence has been reported that suggests that incidence of breast cancer may be affected by OC use in certain subgroups of women. One recent study has suggested that older women who use OCs and also have benign breast disease are at increased risk of developing breast cancer.[43] This question deserves further study, as does that of a possible relationship between OC use and a family history of breast cancer.[44] These subgroups should be identified prior to, rather than as a result of, data analysis. Moreover, because the period at and just after menarche seems so important in the etiology of breast cancer, the possible influence of OC use during this period merits further study.

Possible Mechanisms

Detailed information about the possible mechanisms by which OCs exert the various health effects discussed above would be extremely valuable to both the manufacturers of OC preparations and to physicians and their patients in their choice of contraceptive method. Some of this detailed information could be obtained by more sophisticated epidemiologic studies among very large populations. The cost of such studies, however, would be prohibitive. Consequently, it would be most helpful if the results of current epidemiologic studies were used in the formulation of mechanistic hypotheses relating OCs to various pathologic effects, and if these hypotheses were then tested by combined epidemiologic and experimental investigations.

A variety of questions can be addressed with this approach.

- How do synthetic and natural estrogens and progestins influence the cardiovascular system in ways that may promote hypertension, thrombosis, or atherosclerosis?

- Do estrogens, progestins, or combinations thereof have classical tumor-inducing or tumor-promoting influences on target organs in animal models or cultured cells?

- Are any of the known influences of contraceptive steroids, especially estrogens, on the synthesis of specific proteins related to pathologic processes?

- Do OC users show significant differences in absorption or steady state levels of essential nutrients, particularly vitamins and minerals, compared with nonusers? If so, can these changes be correlated with pathologic processes?

Other Modalities of Steroid Contraception

The concerns and research priorities that are expressed here with regard to oral contraceptives also apply to other modalities of steroid contraception. Depo-medroxyprogesterone acetate (DMPA) is used as a contraceptive to a limited extent in the United States and widely elsewhere in the world. Also, estrogen and estrogen-progestogen preparations are used as postcoital contraceptives. To the extent that is feasible, both of these steroid contraceptive modalities should be evaluated for their effects on vascular and neoplastic disease.

Recommendations for Future Research

- The possible cancer and cardiovascular consequences of long-duration exposure to OCs as well as beginning OC use early in reproductive life should be investigated.

- The interactions between OC use and other cardiovascular or neoplastic risk factors should be quantified.

- The basic mechanisms of OCs in producing cardiovascular disease consequences should be studied.

- Short-term side effects of currently used formulations should be assessed.

III. Intrauterine Devices

In the United States approximately 3 million women are currently using the IUD.[45] The worldwide impact of the IUD on fertility has been substantial. In some countries (Taiwan, Chile, Mexico, Korea, and the People's Republic of China, to name a few), the IUD is apparently the mainstay of the reversible contraception program.[46] Because of its continued use, it has had a substantial impact in lowering fertility in these and other countries. There is less mortality associated with the IUD than with oral contraceptives or with surgical sterilization.[1] With respect to morbidity, however, more hospitalization is caused by the IUD than by the oral contraceptive or surgical sterilization.[47] When one considers the number of people using IUDs and the impact on fertility regulation and also the fact that IUD users suffer preventable illnesses resulting from IUD use, further studies of the effect of the IUD on the user are needed.

Current State of Knowledge

The NICHD has recently completed a multicenter case-control study--the Women's Health Study--of the diseases that may be associated with IUD use. The results of this study, which are briefly summarized below, are being compiled for publication.

- The Women's Health Study reconfirmed many earlier studies[48] that reported the association of IUDs and pelvic inflammatory disease. All major types of currently available IUDs were equally likely to result in this disease, and more hospitalizations for it occurred near the time of insertion of an IUD than at any other time. The study did not examine the bacteriology of pelvic inflammatory disease, nor did it examine specifically the effect of the tail of the IUD on infection rates.

- Women who have used the IUD at some time in their lives and women who have never used the IUD are equally likely to develop ectopic pregnancy. This datum would suggest that the often-observed excess of ectopic pregnancies in IUD wearers[49] is a relative rather than an absolute excess. That is, IUD wearers are more likely than users of oral contraceptives or of other types of contraception to develop an ectopic pregnancy, but less likely than noncontraceptors to develop an ectopic pregnancy.

- The FDA has recently ruled that IUDs should not be inserted during the postpartum period because of excess risk of perforation.[50] The Women's Health Study results show that perforation with the IUD is most likely to occur when the insertion occurs in lactating women around 2 months post partum, presumably because of the marked involution of the uterus that occurs in such women.

- The IUD was not found to be associated with abruptio placentae or placenta previa.

- Women who are pregnant during the second trimester and who also are still wearing their IUDs are at greater risk of suffering spontaneous and septic spontaneous abortions during the second trimester. This finding confirms and extends earlier work.[51]

Needed Research

Depending on the population, the incidence rate of pelvic inflammatory disease for women not using IUDs is between 1 in 100 and 1 in 1,000 per year.[45] Use of an IUD increases these rates twofold to fivefold,[45] and perhaps more so among younger, never pregnant women.[52] Furthermore, pelvic infection, while it is not usually life threatening, has the potential to cause infertility, which can be emotionally devastating. The issue of infertility is now being addressed in studies to evaluate the risk after use of the IUD and other contraceptive modalities.

In addressing the mechanism of how the IUD causes infection, several questions must be asked. How do infectious agents get into the uterus and from there into the fallopian tubes? A likely explanation would be that bacteria ascend along the tail of the IUD.[53] This theory should be substantiated or refuted with bacteriologic and experimental work in vitro, in animals, and in humans.

Another question is which bacteria are of major importance in causing pelvic inflammatory disease. Careful aerobic and anaerobic cultures need to be taken from IUD users and nonusers. Further work should be done to determine whether the uterus is sterile at various times after IUD insertion. At this point, the question of uterine sterility in the presence of the IUD is unresolved.[54,55] If the uterus is not sterile, why isn't it and how can it be made sterile?

While the IUD has been exonerated as a cause of the recent increase in ectopic pregnancies in the United States, it still is associated with relatively more ectopic pregnancies than are other methods of contraception. Thus, another opportunity for future research is to develop an IUD that is more effective in preventing implantation of fertilized ova in the fallopian tubes.

IUD-related infections during pregnancy appear to be prevented when the IUD is removed. No future research is suggested in this area.

The information from the Women's Health Study suggests that only lactating postpartum women are at increased risk of uterine perforation. Since post-partum insertion is common in the developing world and in rural America, the finding of the Women's Health Study should be confirmed.

The following areas represent specific opportunities for future research: (1) There is some evidence that progesterone decreases the inflammatory response of the IUD. In addition, there is evidence that progesterone makes the cervical mucus impenetrable to bacteria. If this finding is confirmed, the possibility that progesterone-containing IUDs reduce pelvic inflammatory disease must be considered. If any other new devices appear to offer this benefit, they should also be evaluated. (2) Which women are at special risk of pelvic inflammatory disease? Biochemical and genetic studies, as well as further epidemiologic investigation, may help determine if there are factors that would predict which women are at risk for pelvic inflammatory disease.

Recommendations for Future Research

High Priority

- By what mechanisms does the IUD cause pelvic inflammatory disease? Is the IUD-containing uterus sterile?
- How do infective agents enter the IUD-containing uterus?
- Which agents are of major importance in causing disease?

Moderate Priority

- Confirm the finding that uterine perforations occurring with post-partum IUD insertions are confined mainly to lactating women, and determine the reason.
- Can a way be found to make the IUD prevent tubal pregnancies as effectively as it prevents uterine pregnancies?
- What subgroups of women, especially younger women, are at special risk of pelvic infection? Do different patterns of treatment alter the chances of possible infertility?

IV. Barrier Methods

After a long period of declining use beginning in the early 1960s, some recent evidence points to increasing popularity of barrier contraceptives in the United States. In 1976, only 19 percent of married couples utilizing some form of contraception were using the diaphragm (4 percent), spermicidal foams (4 percent), or the condom (11 percent).[56] By 1978, however, prescriptions for diaphragms had more than doubled.[57] An additional small but unknown proportion of women use spermicidal creams, jellies, and suppositories.

The directness, simplicity, relative safety, and reversibility of barrier methods seem to account for their growing acceptability in many strata of society. An added attraction is the fact that many of the barrier methods are widely available from commercial sources without need for medical consultation or prescription. Over-the-counter availability is especially important to unmarried teenagers, who constitute the most rapidly growing group of contraceptive users in the United States.

Current State of Knowledge

With the possible exception of cystitis among users of the diaphragm, barrier methods are not associated with known illness, disease, or mortality. The observation of excess cystitis, attributed to pressure of the diaphragm on the urethra, needs further evaluation.[58] Other recent evidence

suggests that barrier methods may protect against cervical cancer[59] and agents associated with venereal disease.[60] Instances of local tissue reaction to chemicals present in spermicides have been reported, but they are rare. Information on the systematic absorption of vaginal spermicides is scanty, but some animal studies have suggested changes in liver chemistry.[56] Other animal studies show no abnormalities, however, and preliminary human data are negative.[61] The question of whether the use of spermicides before implantation or inadvertently in very early pregnancy might lead to miscarriage, perinatal mortality, or congenital malformations is unresolved, but an association seems unlikely.[62]

In well-motivated, informed users, the effectiveness of barrier methods in preventing unwanted pregnancy is very high, approaching rates seen among oral contraceptive and IUD users. In general use, however, pregnancy rates among users of the condom, diaphragm, and spermicide are higher.[1] Because of the range of human factors bearing on the use of barrier methods, pregnancy rates often vary widely in different populations. Computer models of mortality among women using reversible methods indicate that barrier methods carry the lowest risk in all age groups between 15 and 45.[63]

Needed Research

The existing evidence suggesting lethal effects of certain spermicidal barrier contraceptives on gonococci, trichomonas, and herpesvirus 2 in vitro needs expansion to include more spermicidal preparations and more agents of venereal disease. Because in vitro studies may be of limited relevance, in vivo studies should be considered in settings where good followup is possible.

Although limited data exist on the effectiveness of the use of the diaphragm by young women, comparable information on vaginal spermicides is unavailable for teenage populations. Since the use of these methods seems to be increasing among teenagers, it is important to define effectiveness rates for widely available spermicides, and possibly condoms, in a self-selected, motivated population of teenagers.

While it seems likely that the use of barrier contraceptives may protect against the development of cervical cancer and its precursors, the limited evidence needs confirmation and expansion. The issue has special relevance to teenagers because of the evidence implicating patterns of early sexual behavior in the development of cervical neoplasia.

A review of available data concerning miscarriage, congenital malformation, and perinatal mortality as related to prior contraceptive use needs to be conducted. While there are no persuasive data suggesting an association between these reproductive outcomes and the use of barrier methods, the importance of the issue may require new studies.

Recommendations for Future Research

- Studies on the protective effects of barrier contraceptives on venereal diseases, such as gonococcal, chlamydial, and trichomonal infections.
- Studies of the use and effectiveness of barrier contraceptives among sexually active teenagers.
- Studies on the protective effects of barrier contraceptives on cervical dysplasia.
- Studies of fetal and infant outcomes in relation to prior contraceptive usage.

V. Female Sterilization

Of all the methods of fertility regulation in the United States, only female sterilization and barrier methods show increasing acceptance by couples. In 1970, 201,000 sterilization procedures were performed; in 1975, the total was 550,000 and there is no indication of a leveling off. The technique of laparoscopic sterilization has accounted for most of this growth. In this procedure, a special optical instrument 1 cm in diameter is inserted through a small incision in the navel of a woman who has not recently been pregnant. The fallopian tubes are then occluded by one of a variety of means. This procedure has become more popular than postpartum sterilization, which is performed shortly after childbirth when the enlarged uterus holds the tubes high in the patient's abdomen. A small incision is made with ordinary surgical instruments directly into the abdomen. In 1975, there were 168,000 laparoscopic sterilizations and 144,000 postpartum procedures.[64]

With well over 4 million women in the United States having been sterilized, female sterilization is emerging as one of the most widely utilized and underevaluated methods of fertility regulation. Among this expanding population

are young women, of whom 250,000 under 30 were sterilized in 1976. Reversibility of sterilization has become an appropriate concern on the minds of physicians performing the procedures, since women of this group are most likely to seek reversal because of divorce and remarriage. Information concerning the safety, efficacy, and long-term complications of sterilization is available in varying degrees of accuracy and reliability. The purpose of this discussion is to indicate what is known and what needs further documentation.

Current State of Knowledge

There have been several independent studies of the immediate hazards of laparoscopy. The American Association of Gynecologic Laparoscopists (AAGL) has conducted annual retrospective studies of its members' experience, the most thorough of which was for the year 1975.[65,66] In England, a 1-year prospective data collection effort throughout the United Kingdom analyzed 50,000 cases.[67] In Buffalo, N.Y., one hospital's experience of 5,000 cases was recently reviewed.[68]

Efficacy

The 1975 AAGL survey revealed a subsequent pregnancy rate ranging from 1.8 to 7.3 per 1,000 sterilizations, depending upon the technique used. The Buffalo study reported 11 pregnancies leading to a reported rate of 2.2 per 1,000 cases following electrocoagulation. Both these reports, though probably accurate, suffer from incomplete followup of cases. Early studies of electrocoagulation in Baltimore achieved a 91 percent postoperative contact.[69] These studies reported 5 pregnancies in 1,000 cases using one method of electrocoagulation. With the use of another technique of coagulation, 17 pregnancies per 1,000 cases were detected, of which 12 were method failures, as opposed to pregnancies due to operator error or pregnancy at surgery. Studies of the spring clip, also with a 90 percent 1-year followup, revealed 25 pregnancies per 1,000 cases, of which 2 to 6 were attributed to method failure.[70] Subsequent studies of failure rates with sterilization techniques have suffered from followup rates of less than 80 percent, making any conclusions from the data unreliable. A fair assessment of sterilization failure rates for all techniques combined would be 1 pregnancy per 1,000 procedures per year, with differences between techniques very difficult to detect because of followup problems.

Safety

The 1975 AAGL survey, based on 77,000 cases, detected a rate of 3 major complications requiring immediate major surgery per 1,000 cases. Most of these complications were caused by bleeding of the tube after division. The British survey found 12 major complications per 1,000 cases. The report from Buffalo revealed a major complication rate of 4.6 per 1,000 cases, again caused mostly by bleeding. The only study analyzing overall complications, including infections, hematomas, and other nonsurgical problems, reported a complication rate of 30 to 50 per 1,000 cases, varying with the technique of sterilization employed. The traditional coagulation and clip techniques were associated with lower overall complications, compared to the silastic band and tube exteriorization techniques.[67]

The mortality directly related to the procedure was 2.5 per 100,000 cases in the AAGL survey, and 10.4 per 100,000 cases in the British survey. A major contributing factor in such deaths in England and the United States has been complications of general anesthesia. An immediate life-threatening but under-reported hazard of laparoscopy is arterial injury, which has been reported informally to have occurred to date in over 100 instances in the United States.[71]

Cases of delayed surgical complications occurring within 2 weeks of surgery have centered mostly about unsuspected bowel burns at the time of electrocoagulation of the tubes, leading to bowel perforation and generalized abdominal infection. There have been at least 40 such cases in the United States. In terms of rates, they are relatively rare--0.5 per 1,000 cases in the United States; 0.6 per 1,000 in the United Kingdom. Nevertheless, these serious events have stimulated the development of safer electric and nonelectric techniques, such as bipolar coagulation (where the current runs from one tip of the forceps to the other, rather than through the body back to the base plate) and silastic bands and spring clips, which avoid the use of electric current altogether. These techniques, developed and evaluated both with Federal funding and with private support, are replacing the older technique of electrocoagulation with a base plate.

Nosocomial infections are a major concern in surgical procedures and are the reason some hospitals recommend that laparoscopes be sterilized by ethylene oxide gas between cases. This procedure is expensive, time-consuming (8-12 hour cycles), and effectively limits the number of procedures that can be done in a hospital to the number of instruments available. Many hospitals and clinics have performed thousands of operations using disinfection (glu-

taraldehyde soaking for 20 minutes) between cases and have failed to detect any nosocomial infections. The glutaraldehyde solution kills all bacteria, but has not been documented to kill viruses such as those causing hepatitis, and definitely does not kill spore-forming organisms.

Late complications occurring years after the procedure are emerging as a major concern of physicians and their patients, and they have been poorly evaluated to date.

After having had their tubes divided, women have returned to their physicians complaining of irregular uterine bleeding, sometimes with pelvic pain, for which hysterectomies are then performed. The first study of this phenomenon, which used wives of vasectomized men as controls,[72] revealed a 39-percent increase in reported menstrual blood loss after laparoscopic electrocoagulation sterilization. This loss was compared to a 22-percent increase after traditional postpartum surgical division and a 13-percent increase among nonsterilized controls. Other studies of menstrual changes after laparoscopic clip application[73] detected no significant difference if previous methods of contraception (OCs, IUDs) were taken into account. An extensive review of the literature on this subject was performed and reported in 1977.[74] Existing data are difficult to evaluate because of problems in definition and selection of both patients and controls in the reported literature. A thorough, prospective study is needed.

Recently there has been a report of diminished production of progesterone in the second half of the menstrual cycle in sterilized women.[75] These lowered levels were detected in asymptomatic women requesting reversal. These findings are of concern in that they reflect subtle endocrine changes as a result of tubal and peritubal vascular damage. This study is currently being repeated in at least three centers in the United States (Pennsylvania, Tennessee, and North Carolina).

A second area of major concern involves ectopic pregnancy, which is a pregnancy growing other than in the uterus, usually in the fallopian tube. This is a rare but serious late complication of sterilization, since the pregnancy will eventually erode into a neighboring blood vessel and cause acute abdominal hemorrhage. This problem has increased in recent years, mostly due to increases in tubal infection, and it is now the leading cause of maternal death in the United States. A recent review of reported ectopic pregnancy rates associated with fertility regulation methods reveals a wide range of ectopic pregnancies subsequent to laparoscopic sterilization techniques. No ectopic pregnancies have been reported following spring clip application, but a rate of 600 ectopics per 1,000 pregnancies has

been reported with the silastic ring. The standard postpartum surgical tubal division has a rate of 200 ectopics per 1,000 pregnancies.[76] The Buffalo study revealed a rate of 636 ectopics per 1,000 pregnancies after electrocoagulation sterilization; 7 of 11 pregnancies following electrocoagulation were ectopic in the researchers' experience. Ectopic pregnancies can follow sterilization regardless of the technique used. These findings imply that studies of ectopic pregnancies might lead to a technique of female sterilization that will have a minimum risk of causing subsequent ectopic pregnancies.

Reversibility

It has been estimated that 1 percent of sterilized women, or about 6,000 American women a year, will request reversal of sterilization, usually because of divorce and remarriage.[77] Modern techniques of microsurgery, in the best series reported to date, have yielded subsequent pregnancy rates of 40 to 75 percent.[78,79] In these studies, the pregnancy rates were higher when minimal tissue damage was encountered, such as after the clip procedure, and were lowest when maximum tissue damage was encountered, such as after extensive electrocoagulation. To date, however, there has been no analytical study of reversal rates based on sterilization operations originally performed and reversals subsequently requested. Both the British and the AAGL studies have suggested that for patients requesting reversal, fewer come to surgery after coagulation sterilization than after less destructive techniques. Data concerning factors influencing reversibility, including the nature of the original sterilization procedure performed, need to be collected and analyzed from among those women currently seeking reversal.

Comparative Cost-Effectiveness of Different Techniques

Recent enthusiasm by funding agencies for minilaparotomy has led to recommendations that this procedure be performed in clinics instead of in hospital operating rooms, in order to make sterilization more widely available. Early studies comparing this technique to laparoscopy have shown that postoperative infection and pain may be increased with minilaparotomy. The comparative cost-effectiveness and patient acceptance of laparoscopy as opposed to minilapa-

rotomy in both hospital and clinic settings have not been evaluated. In the same category, the cost-effectiveness of recommending elective tubal ligation soon after delivery--before hospital discharge--has never been evaluated in comparison with the increasingly popular laparascopic technique. The Centers for Disease Control in Atlanta are currently collecting such data in the Collaborative Review of Sterilization Study of different types of sterilization procedures. This is being done in an effort to study both the morbidity and the cost in health care dollars.

Needed Research

Prospective Comparative Study With Controls and Followup

A prospective, comparative evaluation of all female sterilization techniques is needed. Such a study should include immediate and delayed surgical complications, as well as a 3-year followup to detect late complications, including menstrual irregularities, nosocomial hepatitis, and pregnancies. A comparison group of unsterilized women should be identified and followed. Among women not sterilized, the cost of needed medical visits, the cost of medications, the risk of pregnancy, and the cost of morbidity associated with abortion could be compared to the costs and risks experienced by the sterilized groups. True benefit-risk ratios could then be generated by proper evaluation of sterilizations and their alternatives.

If the recent suggestion is confirmed that luteal function may be altered by tubal destruction, such prospective studies should include endocrine evaluations of patients before and after sterilization, including serial plasma progesterone levels. Studies of the mechanisms responsible for these altered functions would also be appropriate.

Factors Influencing Reversibility

A number of centers where the reputation for surgical excellence has led to referrals for reversal of sterilization could be asked to record factors prospectively among their patients. Factors to be recorded would include: fertility documentation prior to surgery; type of sterilization originally performed; the details of the tubal destruction present from the previous sterilization procedure; the

details of the anastomosis (reversal) procedure performed, including the amount of isthmus or ampulla found to be remaining and the type of suture; and techniques of pre- and postoperative management. A 3-year followup should be recorded to document the true success rate in terms of live births.

Ectopic Pregnancies

Studies are needed of all pregnancies following a sterilizing procedure. Such an effort would establish the ratios of ectopic pregnancy to intrauterine pregnancy, by method of sterilization.

Recommendations for Future Research

- A prospective, comparative study of all sterilization techniques, in order to evaluate long-term problems such as irregular bleeding, hepatitis, and pregnancy.
- Studies of ectopic pregnancies to determine ectopic-intrauterine pregnancy ratios for currently used methods of sterilization.
- Studies of women seeking reversal of sterilization, in order to determine those factors that influence reversibility.

VI. Male Sterilization

Vasectomy has gained increasing acceptance as a method of permanent contraception both in the United States and throughout the world. In the United States until the late 1960s, contraceptive vasectomy was performed as an office procedure or, less frequently, in a hospital; very few outpatient clinics offered this service. In 1969 and 1970, vasectomy clinics were opened in many cities in the United States, either as independent units or as part of family planning service programs. The number of men accepting the procedure increased markedly, as reflected in information from two sources. Data from the National Fertility Surveys of 1965 and 1970,[80] and the National Surveys of Family Growth in 1973 and 1976,[81] based on interviews in national probability samples of married women of reproductive age, indicate that the husbands of 3.3 percent of the women had

been vasectomized in 1965. This proportion rose to 5.1 percent in 1970, 7.8 percent in 1973, and 9.7 percent in 1976. If only husbands of women age 30 to 44 are considered, the frequency increased from 4.2 percent in 1965 to 14.5 percent in 1976, and for white women age 30 to 44 it reached 15.5 percent in 1976. Estimates of the frequency of vasectomy are also provided by an annual survey conducted among private practitioners, clinics, and military facilities by the Association for Voluntary Sterilization.[82] This survey indicates that 215,000 voluntary male sterilization operations were performed in the United States in 1969, 750,000 in 1970, 700,000 in 1971, and about 500,000 per year since 1971--for a total of over 5 million in the 10 years from 1969 through 1978.

Current State of Knowledge

Efficacy and Side Effects

Vasectomy has been readily accepted because it is simple, inexpensive, effective, and apparently without serious medical consequences either in the immediate postoperative period or over a longer term. The failure rate is very low and ranges from 0 to 6 percent.[83] Failure is attributable to neglecting to identify the vas correctly or neglecting to detect anomalous duplication of the vas, as well as to spontaneous formation of a new channel for the passage of sperm. The recanalization process, documented by study of tissue specimens after reoperation, occurred in six men in one series of 770 vasectomies.[84] Early postoperative complications such as infection, hematoma, epididymitis, and sperm granuloma formation have been reported in 3 to 4 percent of a series of 2,711 vasectomies performed in Houston,[83] and in 12 percent in a British series of 1,000 using somewhat different criteria.[85] Complications are usually mild and of short duration. No serious long-term consequences of vasectomy have thus far been demonstrated in man, but, as indicated below, the possibility of such consequences remains and therefore requires further investigation.[86]

Immune Response

Vasectomy is unusual among surgical procedures in that it involves the potential for inducing an autoimmune reaction. This results from the fact that sperm are not present at birth but develop only at the time of puberty, long after immunologic tolerance for the body's own tissues has been established.

Sperm antigens therefore induce an immune reaction if exposed to immunocompetent cells. Normally, developing sperm cells are sequestered behind tissue barriers, but these barriers are often broken after vasectomy, resulting in exposure of lymphocytes to sperm antigens and development of autoimmunity. It is now well established that from one-half to two-thirds of vasectomized men and experimental animals develop circulating antibodies to sperm after the procedure, and, contrary to earlier reports, no diminution in this response is seen in man at intervals up to 4 years after surgery.[87] This chronic immune reaction is cause for concern, since it offers the potential for a wide variety of pathologic effects.

Long-Term Consequences

Human Studies

Several prospective clinical studies of vasectomized men have been completed.[86] These have involved small numbers of patients, ranging from 50 to 200 per study for a total of over 400 men, and a variety of medical, endocrine, and immunologic tests. Studies were conducted from 2 to 4 years after surgery. The data from these studies are consistent. No clinical consequences of vasectomy have been identified, and the only medically significant laboratory finding appears to be the development of circulating antibodies to sperm antigens. The numbers of men involved in these studies are too small, however, and the period of followup is too brief to identify any rare diseases that might occur as a result of the chronic immune response stimulated by vasectomy. Preliminary data from a Scottish record-linkage study[88] are also negative, but thus far this study involves less than 2,000 vasectomized men who were followed for a mean interval of less than 5 years.

Animal Studies

Two types of testicular disease of immunologic origin have been demonstrated in vasectomized animals. In rabbits with sustained antibody levels after vasectomy, a severe immune complex orchitis has been demonstrated 10 to 20 months after surgery.[89] Immune complexes made up of sperm antigen and antisperm antibody are deposited at the basement membrane of the testicular tubules, and the epithelium with its developing sperm cells is destroyed. Some of the more

severely affected rabbits also showed deposits in the kidneys, suggesting the potential for kidney disease and other sequelae resulting from circulation of immune complexes to distant sites. In guinea pigs, pathologic changes different from those in the rabbit and resembling those of experimental allergic orchitis, a disease of the testis that can be induced by immunizing with sperm, are seen 1 to 2 years after vasectomy but not earlier.[90] Recent studies in 25 rhesus monkeys vasectomized up to 15 years earlier and 13 age-matched controls demonstrated pathology in the testis similar to that in vasectomized guinea pigs, in association with immune complex deposits in the excurrent ducts. The lesions in the testes were seen in 92 percent of the vasectomized monkeys, as compared with 23 percent of the controls.[91] An immunologic basis for the disease in monkey testes appears likely but remains to be established.

Potentially the most serious consequence of vasectomy demonstrated thus far is the marked increase in atherosclerosis in the major arteries of vasectomized monkeys. This finding has come from two separate studies. In the first study,[92] 10 cynomolgus monkeys were fed a diet very high in cholesterol and half of them were vasectomized while the other half were sham-operated. Ten months later, the animals were sacrificed and the extent and severity of atherosclerosis were compared in the two groups. The vasectomized animals demonstrated a marked exacerbation of atherosclerosis, which was apparent by both biochemical and morphological measures and was consistent in several major systems of arteries. There were justifiable doubts about the significance of these findings when originally reported, however, because of the very high level of cholesterol in the diet and the small number of experimental animals.

The second study[93] was conducted in rhesus monkeys maintained on a diet of standard monkey chow, which contains no cholesterol and is very low in fat. Ten monkeys vasectomized from 9 to 14 years earlier were compared with eight age-matched controls. Again, the monkeys were sacrificed for a study of the major arteries, and again the vasectomized animals demonstrated much more extensive and severe atherosclerosis than the controls. The increased atherosclerosis in vasectomized animals presumably resulted from immunologic injury to the walls of the arteries, probably by immune complexes circulating in the blood. The numbers of animals involved in these two studies were small, but they represent two different species of subhuman primates. In the second study, long exposure to the effects of vasectomy apparently caused increased atherosclerosis, even with a cholesterol-free, low-fat diet.

Reversibility

Another important area in the field of male sterilization is surgical reversal of the procedure by reanastomosis of the severed vas (vasovasostomy).[94] As increasing numbers of men are vasectomized, requests for reversal and restoration of fertility are also increasing, frequently because of changed family circumstances. There are numerous reports of small series of vasovasostomies, but success rates are often reported merely in terms of the return of even small numbers of sperm to the ejaculate. Success rates in these terms are generally on the order of 70 percent or better,[95] and in recent publications they reach from 83 to 96 percent.[96] Pregnancy rates achieved, where reported, are much lower, however, recently ranging from 39 to 72 percent.[96] Reasons for the discrepancy between patency rates of the vas and pregnancy rates in the female are not clear, but they may include the experience of the surgeon, the surgical technique used for reanastomosis, the duration of exposure to the effects of vasectomy, continuing effects of the immune response to vasectomy, continuing pathologic effects in the testis, subtle damage to the epithelium of the epididymis, or damage to the nerve supply to the vas and thus to its ability to transport sperm. Microsurgical techniques of reanastomosis may provide some improvement in pregnancy rates, but so far they have not been entirely successful.[95,96]

Ongoing Studies

The Health Status of American Men is a cohort study in which some 15,000 previously vasectomized men are being compared with matched control subjects. The study, designed to identify any increased risks of rare diseases that might occur as the result of a chronic immune response, will provide a followup on vasectomies performed from 1955 to 1976. Tracing and interviewing the subjects in the study, together with validation of medical events and analysis of the data, are expected to be completed late in 1982.

The issue of vasectomy-induced exacerbation of atherosclerosis is being addressed in one study in monkeys and three in man. The monkey study involves 135 vasectomized or sham-operated animals maintained on a moderately atherogenic diet. The extent of atherosclerosis will be assessed in half the animals 18 months after surgery. In the remainder, the possible ameliorative effects of vasectomy reversal and of reduced dietary fat will be evaluated. In man, the possible role of vasectomy in increasing the severity of coronary atherosclerosis is being studied, using existing data on some 10,000 men who have had coronary angiography.

The possible role of vasectomy as a risk factor for myocardial infarction is being evaluated in two recently initiated case-control studies, one utilizing risk factor and outcome data from an exercise-testing registry, and the other a classic, hospital-based case-control study of myocardial infarction in young men. These studies will be completed in 1983.

In addition to the above studies, the question of cardiovascular effects of vasectomy is also being addressed in ongoing studies of smaller populations with unknown prevalence of vasectomy. These include the Multiple Risk Factor Intervention Trial (about 12,000 men), the Sons of Framingham study (about 2,000 men), and a study involving assessment of the extent of peripheral arterial disease in 450 men in San Diego.

Needed Research

Further Followup of Vasectomized Men

The major issues related to the safety of vasectomy concern the possibility of increased risks of immunologic and(or) cardiovascular disease. It is quite possible that the effects of vasectomy may be evident only at very long intervals after surgery, as suggested by the increase in atherosclerosis in monkeys from 9 to 14 years after surgery. (Rhesus monkeys have a life span of about 20 years in the wild and 35-40 years in the protected environment of a primate colony.) The cohort study of the Health Status of American Men will provide, according to current plans, a onetime followup of some 15,000 men vasectomized between 1955 and 1976, plus an equal number of matched control subjects. The study has required a major effort in tracing vasectomized and control subjects, and although final success rates are not yet available, preliminary data indicate they will be very high. The value of planning for reinterview of these subjects after completion of the initial study is becoming increasingly apparent. The duration of followup could be substantially extended at minimal cost, since the major work of tracing will have been completed and an abbreviated interview would be sufficient to update the data already collected.

Reversibility

Another major issue related to vasectomy, and one that has not yet been addressed, is the lack of success in

reversal of the operation and restoration of fertility. A collaborative clinical effort is suggested to determine fertility rates achieved in various circumstances and to identify factors that may contribute to success or failure. A number of centers with experience in vasectomy reversal by macrosurgical and microsurgical techniques should be enlisted to follow a common protocol in evaluating patients before and after reanastomosis. Studies suited to the expertise of individual contributing groups should be conducted in central laboratories in an effort to determine the roles played by such factors as immune reactions to vasectomy, postvasectomy testicular pathology, epididymal function, and vas motility. Investigations to clarify the nature of the testicular disease seen in vasectomized monkeys and guinea pigs and to determine if similar pathology occurs in vasectomized men could also contribute to solving the problem of infertility following reanastomosis.

Pathologic Mechanisms Involved in Postvasectomy Atherosclerosis

Research is also needed to clarify the mechanisms involved in the exacerbation of atherosclerosis identified in vasectomized monkeys, which may occur in man. While it is assumed that immune complexes circulating in the blood are responsible for initiating the atherosclerotic process, this phenomenon has not yet been demonstrated, and another possibility has recently arisen. An antigen of glycolipid structure (that is, composed of carbohydrate and fatty acid) has now been isolated from guinea pig sperm.[97] The glycolipid nature of this antigen has important implications, since the lipid (fatty acid) portion of circulating antigen molecules may be readily inserted into the walls of cells lining the arteries, and make them targets for injury by antibody and complement and initiate plaque formation. The presence of circulating immune complexes would not then be required. Studies are in progress to determine if antibodies to this glycolipid antigen can be demonstrated in vasectomized men. If they can, the finding should be followed up actively. It could contribute significantly to knowledge of immunologic mechanisms of atherosclerosis in general, and could lead to a preventive immunization against postvasectomy atherosclerosis.

Recommendations for Future Research

- Further followup of subjects in the cohort study Health Status of American Men.

- A collaborative clinical study of vasectomy reversal and factors involved in failure to restore fertility.

- Pathologic mechanisms involved in postvasectomy atherosclerosis.

VII. Summary of Recommendations

A few general points should be made about issues that do not lend themselves to specific research recommendations but are important to the entire research effort and relate to the assumptions upon which many of the specific recommendations are based.

First, there is a continuing need in research on contraceptive development to remain responsive to new contraceptive methods that may be developed. It is not possible to make a specific recommendation about new methods, since no one can foretell either what the new developments may be or what aspects of their use might be in greatest need of evaluation.

Another area requiring continual surveillance involves the findings from studies currently in progress. It is assumed that these studies will receive continued support until their anticipated dates of completion, and no recommendations pertaining to the objectives of research in progress have been made. Equally important is the point that the results of these studies cannot be anticipated at present. Whatever they may be, they will form the basis for a new set of research inquiries. Again, no specific recommendations in response to currently unavailable data could be made, but studies must be monitored in order to initiate research in response to new information derived from ongoing research.

It should be noted that the past research and research recommended for the future focus on the adverse sequellae of methods for fertility control. These issues must be addressed within a strong scientific framework in order to provide accurate information for users and for providers of the various contraceptive methods. The purpose of addressing adverse effects is to assist the user and the provider in making intelligent choices among a number of methods in order to select the one most appropriate for a particular person.

Sixteen high-priority research recommendations have been formulated. These were selected from among the recommendations listed at the end of each section devoted to a

substantive topic. Within each topic, each recommendation has received a priority rating and is listed accordingly at the end of this summary.

A number of criteria have been used in developing the high-priority recommendations. Study results were weighed in terms of their potential contribution to elucidating preventable mortality, serious morbidity, and lesser degrees of morbidity. For example, previous studies of oral contraceptives have revealed that certain population subgroups, such as women over 40 who smoke, are subject to an increased risk of death and serious cardiovascular complications if they use oral contraceptives. Although the actual number of women affected is small, these adverse events are so serious that changes in prescribing for this subset of women are taking place. The continuation of the followup study of vasectomized males is recommended because of a possible acceleration of the rate of development of atherosclerotic manifestations, or the possible occurrence of other as yet unidentified diseases. Since serious morbidity is at issue, the study assumes high priority. Although the infections associated with the use of intrauterine devices are less serious, they occur with relatively high frequency so that their overall effect is large. Therefore, infection associated with intrauterine devices is a problem with high priority for further investigation. In each example cited, the potential for reduction in mortality and morbidity is a significant feature of the research results.

Another consideration in developing high-priority recommendations is the number of women or men affected. Those contraceptive methods that have the greatest frequency of use, and therefore affect the most people, deserve particular consideration. Changing trends in the popularity of different methods also must be noted. For example, increased reliance on female sterilization during the past decade creates a need for more information about possible adverse effects from these procedures.

The availability of existing data about particular methods or procedures has also been noted. Adverse effects of oral contraceptives have been researched extensively during the past decade, whereas female sterilization has received little attention. Other examples of neglect are the traditional barrier methods. Since these may be particularly suitable for the teenage population, which is in great need of appropriate contraception, the possible beneficial effect of these methods in preventing venereal infections requires investigation. The practical effects of the research findings have also been considered. Research that might change user and provider behaviors has been given higher priority. Prevention of venereal infections by barrier methods should increase the acceptability of these

methods among persons at high risk of infection. Another example of high-priority research is the issue of potential reversibility after certain types of sterilization procedures. If reversibility is possible, physicians will have less hesitancy to perform these procedures, thereby making them more readily available. Hence, the need arises for evaluating the reversibility of various sterilization techniques.

In view of these considerations, 16 high-priority recommendations follow.

Oral Contraceptives

- Investigate the possible cancer and cardiovascular consequences of using OCs over a long duration, as well as of beginning OC use early in reproductive life.
- Study the basic mechanisms of OCs in producing cardiovascular disease consequences.
- Quantify the interactions between OC use and other cardiovascular risk factors.
- Assess the short-term side effects of currently used formulations.

Intrauterine Devices

- Study the mechanisms whereby IUDs cause pelvic inflammatory disease.
- Evaluate the findings that uterine perforations are confined to IUD insertions in postpartum lactating women.
- Study how IUDs can prevent tubal pregnancies as effectively as intrauterine pregnancies.

Barrier Methods

- Study the protective effects of barrier contraceptives against venereal disease.
- Evaluate the use effectiveness of barrier contraceptives among sexually active teenagers.
- Study the protective effect of barrier contraceptives on cervical dysplasia.

Female Sterilization

- Evaluate long-term problems associated with all sterilization techniques including irregular bleeding, hepatitis, and pregnancy.
- Determine those factors influencing reversibility among women seeking reversal of sterilization.
- Determine ectopic/intrauterine pregnancy ratios for currently used methods of sterilization.

Male Sterilization

- Continue followup of subjects in the cohort study of the Health Status of American Men.
- Sponsor a collaborative clinical study of vasectomy reversal and factors involved in failure to restore fertility.
- Identify pathologic mechanisms involved in post-vasectomy atherosclerosis.

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